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MINI REVIEW

DOSE-RESPONSE RELATIONSHIP IN TOBACCO-RELATED CANCERS OF BLADDER AND LUNG: A BIOCHEMICAL INTERPRETATION

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The purpose of our study is to address the challenge of evaluating carcinogenic effects at low levels of exposure to carcinogens. We examine the shape of the dose-response relationship between tobacco smoking and cancers of the bladder and lung, and the implications for the evaluation of the effects of exposure at lower levels, for example, environmental tobacco smoke (ETS).

DOSE-RESPONSE RELATIONSHIPS IN TOBACCO CARCINOGENESIS: BLADDER AND LUNG CANCER

The fact that low doses of tobacco may have a carcinogenic effect proportionally greater than high doses is suggested by the study of dose-response relationships. A previous study, based on the re-analysis of a multicenter case-control study on lung cancer and of several studies on bladder cancer,[1] suggested that the dose-response relationship between cigarette smoking and cancer risk tends to level off after a dose of approximately 20–25 cigarettes/day. A few explanations were put forward to explain leveling off, including bias (less accurate reporting by heavy smokers with cancer), lower inhalation at high doses or genetic heterogeneity of the population, with a "depletion of susceptibles" at low-dose levels. To test the latter hypothesis, we have reviewed the recent studies on smoking and bladder cancer, a type of tumour that is particularly well studied from a biochemical-molecular point of view (Tables I and II).

We have identified all the cohort or case-control studies on smoking and bladder cancer published from 1985 to 2002 (those published before were reviewed in the IARC Monograph on tobacco smoking[2]). We have considered men only because data for women tended to be unstable. We have extracted dose-response data, showing odds ratios and 95% confidence intervals whenever possible. Table I shows the results of case-control studies, and Table II those of cohort studies. Virtually all studies, except 1 case-control (Momas *et al.,* 1994) and 2 cohort studies (Engeland *et al.,* 1996; Tulinius *et al.,* 1997), show a leveling off after 20–30 cigarettes/day. Engeland *et al.* (1996) and Tulinius *et al.* (1997) show an attenuation of the slope but not a clear leveling off. The consistency between the 2 different designs suggests that we are observing a real phenomenon and not an artifact because different types of bias occur in case-control and in cohort investigations. In fact, only the former design is prone to retrospective recall bias, with underestimation of heavy consumption by cancer cases.

There are other examples in the literature in which the shape of the dose-response relationship levels off. The relationship between TCDD (dioxin) exposure (measured in the plasma of the exposed workers) and total mortality from cancer[3] shows a plateauing of the curve, *i.e.,* an effect that is proportionally greater at lower levels of exposure. Other examples are liver tumours and vinyl chloride in rats[4] or lung cancer and arsenic in humans.[5] However, it should be noted that these are heterogeneous situations, concerning both mutagens like vinyl chloride and chemicals like TCDD and arsenic that have multiple mechanisms of action, such as Ah receptor induction or DNA repair inhibition.

Lung cancer shows a similar pattern but not consistently. As Table III shows, leveling off is present in some studies (Stellman *et al.,* 1998 and 1989; Kuller *et al.,* 1991; Engeland *et al.,* 1996; Nordlund *et al.,* 1999) but not in others (Chow *et al.,* 1992; Potter *et al.,* 1992; Freund *et al.,* 1993; Islam *et al.,* 1994; Tulinius *et al.,* 1997).

HYPOTHESIS

It has been suggested that bladder cancer in smokers may be mainly attributed to arylamines contained in tobacco smoke, such as 3-aminobiphenyl and 4-aminobiphenyl.[6,7] Arylamines are metabolized by enzymes encoded by polymorphic NAT-1 and NAT-2 genes.[8] Such genes are involved in the detoxification of mononuclear arylamines, in particular 2-naphthylamine and 4-aminobiphenyl. The genetically based slow acetylator phenotype implies slower detoxification, *i.e.,* higher levels of DNA adducts from arylamines, and a higher risk of bladder cancer.[9] In addition, we have hypothesized in the past that the effect of the NAT-2 genotype can be greater at low levels of exposure.[9] In other words, our hypothesis is that subjects with the slow acetylator phenotype tend to diverge from rapid acetylators more at low levels of dose than at high levels (the explanation of this phenomenon is reported below). This means that *(i)* there is a dose-response relationship in both rapid and slow acetylators, *i.e.,* in both the risk increases with an increasing number of cigarettes smoked; *(ii)* slow acetylators in general have a greater risk of bladder cancer; *(iii)* the difference between slow and rapid acetylators is more evident at low doses. If this is true, then the admixture of slow and rapid acetylators in the general population (with approximately 50% subjects for each genotype, *i.e.,* a high frequency of slow acetylators) would imply a leveling off of the risk of bladder cancer at higher doses. The first two statements are generally agreed upon, while the third is more controversial. We have described this effect previously in separate publications[9,10] as the low-dose effect or the inverse effect of genetic susceptibility polymorphisms. What follows is an explanation of one of the biochemical mechanisms that could be responsible for the low-dose effect.

BIOCHEMICAL BASIS FOR A LOW-DOSE EFFECT OF GENETIC SUSCEPTIBILITY

If a genetic polymorphism (or 1 of 2 or more possible alleles) results in a gene product with a higher enzymatic activity (such as

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TABLE I – CASE-CONTROL STUDIES ON NEWLY DIAGNOSED BLADDER CANCER (MEN ONLY) ODDS RATIOS [95% CONFIDENCE INTERVALS] FOR DAILY CIGARETTE CONSUMPTION

Authors	No. of cases	Dose	OR (95% CI)	Comments
Harris *et al.* 1990, USA	1,114 whites	1–10	1.5 (1.1–2.2)	Hospital-based; adjusted for age, years since quitting, education
		11–20	3.0 (2.5–3.7)	
		21–30	3.7 (3.9–4.5)	
		30+	3.6 (3.0–4.4)	
	84 blacks	1–10	1.6 (0.7–3.6)	Hospital-based; adjusted for age, years since quitting, education
		11–20	1.9 (0.9–3.9)	
		21–31	2.7 (1.1–6.6)	
		30+	2.0 (0.7–5.9)	
De Stefani *et al.* 1991, Uruguay	91	1–14	4.7 (1.3–16.9)	Hospital-based; adjusted for age, residence, SES
		15–29	11.5 (3.3–40.6)	
		30+	8.2 (2.2–30.2)	
Kunze *et al.* 1992, Germany	531	1–9	1.7 (1.1–2.5)	Hospital-based; adjusted by age and sex
		10–19	2.5 (1.7–3.6)	
		20–29	3.6 (2.4–5.4)	
		30–39	9.3 (4.3–20)	
		40+	1.9 (1.1–3.5)	
Vena *et al.* 1993, USA	351	0–2	1.0 (ref)	Population-based; adjusted for age, coffee, sodium, diet
		3–28	1.7 (1.1–2.6)	
		29–48	2.1 (1.4–3.1)	
		49–144	2.7 (1.8–4.0)	
Momas *et al.* 1994, France	219	<365[1]	1.0	
		365–146,000	3.4 (1.5–7.8)	
		146,001–320,000	5.0 (2.4–10.7)	
		>320,000	8.7 (4.2–17.8)	

[1]Total cigarettes smoked.

TABLE II – COHORT STUDIES BASED ON INCIDENCE OR MORTALITY DATA (MEN ONLY) ODDS RATIOS FOR BLADDER CANCER [95% CONFIDENCE INTERVALS OR NUMBER OF CASES] FOR DAILY CIGARETTE CONSUMPTION

Authors	Size cohort and follow-up duration	Dose	Relative risk (95% CI)	Comments
Steineck *et al.* 1988, Sweden	16,477	1–9	4.5 (2.1–9.9)	Adjusted by age; short follow-up
	1969–82 (incidence)	10+	4.7 (2.0–10.8)	
McLaughlin *et al.* 1995, USA	250,000	1–9	1.1 (0.8–1.5)	US veterans; adjusted for age and calendar period
	26 years (mortality)	10–20	2.3 (1.9–2.7)	
		21–39	2.7 (2.2–3.3)	
		40+	2.2 (1.5–3.3)	
Akiba *et al.* 1990, Japan	122,261	1–4	1.8 (0.4–5.0)	Adjusted for residence, age, occupation, observation period
	16 years (mortality)	5–14	1.4 (0.9–2.3)	
		15–24	2.0 (1.3–3.3)	
		25+	1.7 (0.6–4.1)	
		35+	2.1 (0.5–6.1)	
Mills *et al.* 1991 USA	34,198	1–14	1.61 (0.63–4.09)	Adjusted for age and sex; short follow-up
	1976–82 (incidence)	15–24	4.28 (1.90–9.67)	
		25+	3.32 (1.28–8.60)	
			Mortality rates/10,000	
Kuller *et al.* 1991, USA	361,662 (mortality)	0	1.6 (39)	Adjusted for age, pressure, cholesterol, ethnicity
		1–15	1.8 (5)	
		16–25	3.1 (13)	
		26–35	4.4 (12)	
		36–45	3.9 (9)	
		46+	3.6 (3)	
Chyou *et al.* 1993, Hawaii	8,006	>0–30	2.12 (1.19–3.79)	Adjusted "for relevant variables"
	19 years (incidence)	30+	2.30 (1.30–4.06)	
Engeland *et al.* 1996, Norway	26,000	1–4	2.5 (1.5–4.0)	Age-adjusted
	28 years (incidence)	5–9	2.7 (1.6–4.5)	
		10–14	3.4 (2.1–5.4)	
		15+	5.1 (3.1–8.4)	
Tulinius *et al.* 1997, Iceland	11,366	1–14	1.49 (0.74–2.99)	Age-adjusted
	1968–95 (incidence)	15–24	2.59 (1.42–4.74)	
		25+	4.6 (2.37–6.91)	

the fast acetylation for NAT2), it can be shown that the level of increased activity will be higher at lower doses. This reflects the low-dose effect referred to in the previous section and often observed in case-control studies of the effects of certain genetic polymorphisms in metabolic genes on cancer. If the effect of the polymorphisms is dependent on the kinetics of metabolism (Km) of an enzyme-mediated reaction, the low-dose effect should in fact always be seen.[10] To prove this point, we define Y as the ratio:

$$\frac{V_{1p}/V_{1w}}{V_{2p}/V_{2w}} \quad (1)$$

where v_{1w} is the catalytic rate at a low dose for the wild-type enzyme, v_{1p} is the rate at the low dose for the polymorphic enzyme and v_{2w} and v_{2p} are the respective rates at a higher dose. The low-dose effect is defined by $Y>1$. Substituting equation 1 into the Michaelis Menten equation

TABLE III – COHORT STUDIES BASED ON LUNG CANCER INCIDENCE OR MORTALITY DATA. RELATIVE RISK [95% CONFIDENCE INTERVALS OR NUMBER OF CASES] FOR DAILY CIGARETTE CONSUMPTION; MEN AND WOMEN

Authors	Size cohort and follow-up	Dose: cigarettes/day	Relative risk (95% CI) or SMR (no. of cases) or age-adjusted rates per 1,000		Comments
			Men	Women	
Garfinkel and Stellman, 1988, USA	619,225 women 1982–1986 (mortality)	Duration			Authors: As women have begun to smoke earlier in life, smoke more cigarettes per day and inhale more deeply, we are now observing much higher SMRs in women with lung cancer, similar in magnitude to those in men in earlier studies.
		(21–30 years)			
		Nonsmoker		1 (reference)	
		1–10		2.9 (3)	
		11–19		6.7 (3)	
		20		13.6 (16)	
		21–30		18.4 (9)	
		31+		18.9 (7)	
		(31–40 years)			
		1–10		7.9 (18)	
		11–19		19.2 (22)	
		20		19.2 (59)	
		21–30		26.5 (36)	
		31+		25.3 (27)	
		(41–70 years)			
		1–10		10.0 (29)	
		11–19		17.0 (23)	
		20		25.1 (83)	
		21–30		34.3 (36)	
		31+		38.8 (30)	
		Inhalation			
		Nonsmokers		1 (reference)	
		Noninhalers		6.9 (25)	
		Slight		15.2 (72)	
		Moderate		18.5 (252)	
		Deep		31.9 (84)	
Stellman et al., 1989, USA	120,000 male current smokers, 1959–1972 (mortality)	Low tar	SMR		Authors: The excess lung cancer risk for current smokers was directly proportional to the estimated total milligrams of tar consumed daily.
		1–19	524 (20)		
		20	917 (32)		
		21–39	1,086 (25)		
		40+	1,100 (16)		
		Medium tar			
		1–19	768 (87)		
		20	1,053 (131)		
		21–39	1,414 (95)		
		40+	1,824 (66)		
		High tar			
		1–19	717 (62)		
		20	1,281 (140)		
		21–39	1,560 (88)		
		40+	1,930 (60)		
Kuller *et al.,* 1991, USA	361,662 men screened for MRFIT (mortality)		Age-adjusted rates/10,000		
		Nonsmoker	19.2		
		1–15	49.5		
		16–25	111.8		
		26–35	140.4		
		36–45	189.0		
		≥46	205.1		
Chow *et al.,* 1992, USA	17,818 men; 1966–1986 (mortality)	Never	1.0 (reference)		Authors: A non-significant protective effect of lung cancer death was observed for higher dietary intake of vitamins A and beta-carotene
		1–19	15.1 (5.9–38.4)		
		20–29	23.8 (9.5–59.5)		
		30+	48.4 (19.0–123.7)		
Potter *et al.,* 1992, USA	41,843 women; 1985–1988 (incidence)	Pack-years			Author: Those who drank 1 or more beers per week had an odds ratio of 2.0 (1.02–3.80) compared to those consuming less than one beer.
		Never		1	
		<20		2.7 (1.0–6.9)	
		20–39		11.6 (5.9–23.3)	
		>40		22.4 (12.0–42.2)	
Freund *et al.,* 1993, USA	5,209 men and women; 1948–1982 (incidence)		Age-adjusted rates/1,000	Age-adjusted rates/1,000	Author: results from the Framingham Study after 34 years of follow-up.
			45–64 years old	45–64 years old	
		Never	0	0.2	
		1–10	0	0	
		11–20	1.6	0.3	
		21–30	2.1	1.3	
		>30	4.3	1.6	
			65–84 years old	65–84 years old	
		Never	0.5	0.4	
		1–10	4.2	0.9	
		11–20	4.7	2.7	
		21–30	4.7	2.8	
		>30	3.1	—	

TABLE III – COHORT STUDIES BASED ON LUNG CANCER INCIDENCE OR MORTALITY DATA. RELATIVE RISK [95% CONFIDENCE INTERVALS OR NUMBER OF CASES] FOR DAILY CIGARETTE CONSUMPTION; MEN AND WOMEN (CONTINUED)

Authors	Size cohort and follow-up	Dose: cigarettes/day	Relative risk (95% CI) or SMR (no. of cases) or age-adjusted rates per 1,000		Comments
			Men	Women	
Sidney *et al.*, 1993, USA	79,946 men and women, 1979–1985 (incidence)	Tar content of cigarette			Author: The tar yield of the current cigarette brand was unassociated with lung cancer incidence.
		<11 (reference)	1.0	1.0	
		11–18	1.29 (0.69–2.43)	0.93 (0.55–1.59)	
		>18	1.27 (0.67–2.43)	0.67 (0.34–1.32)	
Islam *et al.*, 1994, USA	2,099 women and 1,857 men; 1967–1987 (incidence)		Age-adjusted rates/1,000 present years	Age-adjusted rates/1,000 present years	Authors: Rapidly declining ventilatory function in conjunction with persistent symptoms of chronic bronchitis in current smokers is predictive of an increased risk of lung cancer and correlates with cumulative levels of exposure to cigarette smoke.
		Never	0.56	0.16	
		Former	1.22	—	
		1–19	1.34	0.41	
		20–39	2.00	1.26	
		40+	5.17	2.01	
			No symptoms		
		1–19	0.67		
		20–39	1.18		
		40+	3.90		
			Phlegm and cough >3 months/ year		
		1–19	-		
		20–39	4.25		
		40+	12.31		
Engeland *et* al., 1996, Norway	26,000 men and women; 1966–1993 (incidence)	Never	1 (reference)	1 (reference)	Authors: A higher risk of lung cancer was found for cigarette-smoking women who started cigarette smoking before the age of 30 compared to similar groups of men.
		1–4	1.4 (0.6–3.7)	12 (4.5–32)	
		5–9	4.1 (1.7–10)	12 (4.4–30)	
		10–14	7.0 (2.9–17)	24 (9.5–59)	
		15–19	11 (4.2–28)	26 (9.2–73)	
		≥20	15 (6.1–37)	Too few cases	
Tulinius *et al.*, 1997, Iceland	11,580 women and 11,366 men; 1968–1995 (incidence)	Never	1 (reference)	1 (reference)	Authors: Lung cancer risk is twice as strong for females as it is for males.
		Former	2.91 (1.47–5.74)	3.73 (1.73–8.07)	
		1–14	6.49 (3.25–13.0)	9.39 (4.99–7.7)	
		15–24	13.5 (7.08–25.6)	30.7 (16.8–56.0)	
		25+	28.7 (14.5–55.1)	44.1 (21.1–91.8)	
Nordlund *et* al., 1999, Sweden	56,000 men and women, 1961–1989 (incidence)	Never	1 (reference)	1 (reference)	Authors: These results suggest that men and women have similar relative risks of smoking-related cancers at different levels of smoking.
		<5	1.63 (0.61–4.34)	2.11 (1.17–3.78)	
		6–15	4.39 (2.52–24.33)	6.28 (3.95–9.98)	
		16–25	14.18 (8.27–24.33)	10.27 (5.34–19.77)	
		<26	17.9 (11.14–28.82)	16.45 (7.02–38.54)	

$$V = \frac{SV_{max}}{S + K_m} \quad (2)$$

We have

$$Y = \frac{\{S_1V_p/(S_1 + K_p)\}\{S_2V_w/(S_2 + K_w)\}}{\{S_1V_w/(S_1 + K_w)\}\{S_2V_p/(S_2 + K_p)\}} \quad (3)$$

where S_1 is the low dose, S_2 the high dose, V_w the V_{max} and K_w the Km for the wild-type, with V_p and K_p for the polymorphism. This equation simplifies to

$$Y = \frac{(S_1 + K_w)(S_2 + K_p)}{(S_1 + Kp)(S_2 + Kw)} \quad (4)$$

Note that the dose effect is not seen when the effect of the polymorphism is solely on V_{max} but will be seen when the effect is on Km. Assuming that $S_2/S_1 > 1$, and that $K_p/K_w < 1$, it can be shown that Y is always > 1.

The behaviour of Y as a function of dose is shown in Figure 1. The graph is a plot of rate/V_{max} (which is a function of the dose) *vs.* Y (the extent of the low-dose effect). For this model, $V_w = V_p = 100$, $K_w = 10$, $K_p = 1$, and the high dose was twice the low dose. Doses ranged from 0.01 ($0.001 \times V_{max}$) to 5,000 ($0.998 \times V_{max}$).

If $Y = 1$, then no dose effect would be seen. If Y were less than 1, then there would be a high dose effect, but this does not happen if only the value of Km is affected by the genetic variant. Note that $Y = 1$ at very low doses and also at high doses when v is close to V_{max}. Everywhere else, $Y > 1$ (low-dose effect.) The maximum value for Y is found when $S_1S_2 = K_wK_p$. The shape of the curve depends on the values chosen for K_w, K_p, and the ratio of the high to low dose. Therefore, the low-dose effect is always predicted based on basic enzymology, if the result of the polymorphism is to increase enzyme activity by a decrease in Km.

DISCUSSION

The observation that the risk of bladder cancer in smokers did not increase linearly with the number of cigarettes smoked[1,2] is interpreted here as the consequence of the admixture of 2 subpopulations with different degrees of susceptibility to tobacco carcinogens: slow acetylators, which would be more susceptible to low levels of exposure, and rapid acetylators. In the case of bladder cancer, such interpretation is plausible because it is hypothesized that the result of the "rapid" genotype is to increase enzyme activity by a decrease in Km (kinetics of metabolism). In such cases we always expect a "low-dose effect" of a genetic polymorphism, which is particularly evident when the polymorphism is

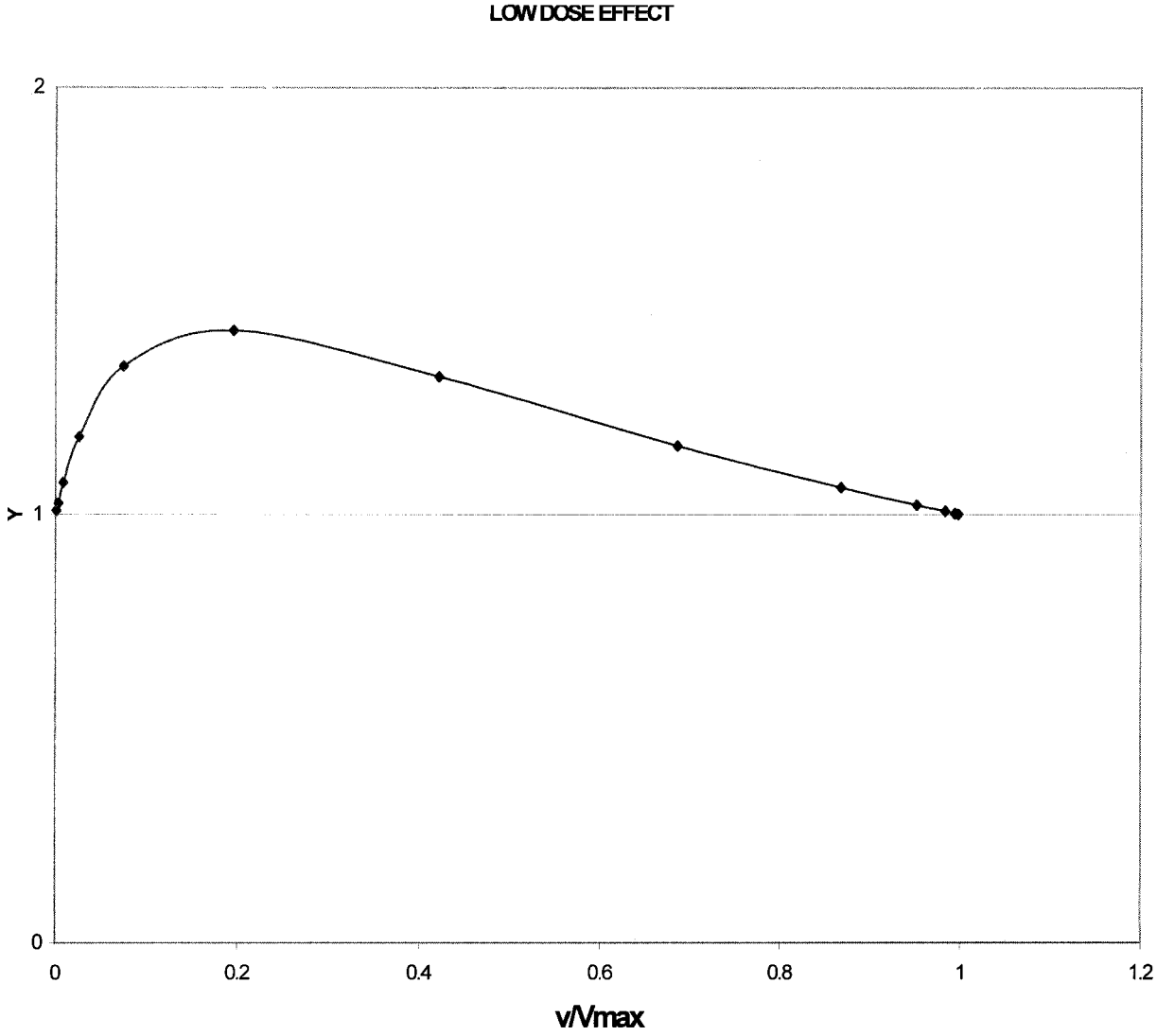

FIGURE 1 – Hypothetical example: the graph is a plot of rate/V_{max} (which is a function of the dose) *vs.* Y (the extent of the low-dose effect).

frequent in the population (50% of rapid acetylators among Caucasians).

Obviously the real dose-response relationship for a complex disease like cancer with any exposure cannot be explained simply using Michaelis-Menten kinetics. Rather what we have tried to demonstrate is the enzyme kinetic basis for the low-dose effect, whereby the presence of a genetic polymorphism in a metabolizing gene leads to a relatively higher effective dose of a chemical carcinogen at lower levels of exposures. The argument is based on initial rates of reaction, at doses below that of saturation. When saturating conditions are found, the effect of the polymorphism (or the intrinsic activity of the enzyme) becomes less important, since enzyme activity remains the same for all phenotypes. In addition, the dose-response relationship for bladder cancer suggests a decrease in risk after plateauing, which is not explained by enzyme saturation as described by Michaelis-Menten kinetics.

A more complex picture emerges when considering lung cancer. In this case the evidence of a leveling off of the risk is weaker: although in a multicenter European case-control study a leveling off was observed,[2] our review of the recent studies (Table III) suggests that only in some investigations the same occurs. This could be due to the more complex intertwining of different metabolic pathways in lung carcinogenesis, including Phase I and Phase II enzymes with the corresponding gene polymorphisms.

There are several important implications of our biochemically based hypothesis. The most important implication is for risk assessment. If several carcinogens are metabolized in ways that are similar to those followed by arylamines, we can expect curvelinear dose-response relationships in carcinogenesis to be more frequent than generally hypothesized, which implies a more important role for low-level carcinogenic exposures than would otherwise be expected.

For example, the carcinogenicity of ETS, clearly established in epidemiologic studies, could be attributed to the existence of a subpopulation of subjects more susceptible to low levels of exposure. More than 50 studies of ETS and lung cancer risk in never smokers, especially spouses of smokers, have been published during the last 25 years. These studies have been carried out in many countries and most showed an increased risk, especially for persons with high exposure (see www.iarc.fr). Meta-analyses have been conducted in which the relative risk estimates from the individual studies are pooled together. They show that there is a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to ETS from the spouse who smokes. The excess risk is in the order of 20% for women and 30% for men, which remains after controlling for bias and potential confounding. The excess risk increases with increasing exposure.[11]

There is strong evidence of the carcinogenicity of ETS in humans. However, it is not clear whether the quantitative evidence on the extrapolation from the high doses of active smokers to the low doses of nonsmokers exposed to ETS is actually consistent. A cigarette equivalent of 0.2/day (range 0.1–1.0) has been estimated when a comparison of log-linear trends in relative risk was made with the number of cigarettes smoked per day in active smokers and in spouses of nonsmokers.[12] This means that nonsmokers exposed to ETS should have an exposure level that is 1/100 of the exposure of a heavy smoker of 20 cigarettes/day. In fact, exposure to ETS is estimated to be 1/100–1/300 of the exposure of an active smoker, *i.e.,* probably lower than the figure based on the epidemiologic extrapolation. In addition, Hecht *et al.*[13] have measured urinary metabolites of the tobacco-specific carcinogen NNK and have found that never smokers exposed to ETS have 2–5% levels of active smokers, a higher level than expected on the basis of the exposure level. Bennett *et al.*[14] have found that, when compared to never smokers who had no ETS exposure, never smokers with exposure to ETS who developed lung cancer were more likely to be deficient in GSTM1 activity (*i.e.,* were GSTM1 null) (odds ratio = 2.6; 95% confidence interval 1.1–6.1). Therefore, it is not unreasonable to hypothesize that the observed relative risks in lifetime nonsmokers exposed to ETS are due to a subpopulation of more susceptible individuals.

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